Pericardial effusion secondary to epicardial undifferentiated pleomorphic sarcoma in a young cat

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Abstract

Case summary A 6.4 kg 3-year-old male neutered indoor–outdoor domestic shorthair cat was referred for further evaluation of non-resolving lethargy and hyporexia of 4 days' duration. Physical examination identified tachypnea with mild respiratory effort and muffled lung sounds bilaterally. Point-of-care ultrasound revealed a large volume of pleural and pericardial effusion (PCE), which was confirmed by thoracic radiography. Echocardiogram indicated normal cardiac function but revealed a mass-like structure along the left epicardium within the pericardial space. After 72 hours in hospital, re-evaluation via echocardiogram showed the epicardial mass lesion to have doubled in size and with apparent extension to involve the pericardium. The patient was hospitalized for 72 h of supportive care and intervention, including therapeutic pericardiocentesis, bilateral thoracocentesis, thoracic and cardiac imaging and infectious disease testing. On the third day of hospitalization, the patient developed cardiac tamponade. Further workup was discussed, including CT and subtotal pericardiectomy with biopsy, but the cat was euthanized due to clinical decline and rapid re-accumulation of effusion. Post-mortem histopathologic evaluation diagnosed an epicardial pleomorphic sarcoma, exclusive of mesothelioma or histiocytic sarcoma on immunohistochemistry (IHC).
Relevance and novel information This report describes a case of epicardial undifferentiated pleomorphic sarcoma (UPS) in a young cat presenting with pleural and PCE. Pleomorphic sarcoma is a rarely reported mesenchymal neoplasia in the feline patient and has thus far primarily been identified in peripheral soft tissue structures. IHC is key to the correct histopathologic diagnosis. To our knowledge, epicardial UPS has not been previously reported in a cat.

Keywords: Sarcoma; cardiac; pericardial; effusion; pleomorphic

Case description

A 6.4 kg 3-year-old male neutered indoor–outdoor domestic shorthair cat was presented to the emergency department for further evaluation of lethargy and hyporexia of 4 days' duration. The cat was evaluated twice by the primary care veterinarian the week prior to presentation. At the first visit, a complete blood count (CBC) revealed mild thrombocytopenia (169×10^3/µl; reference interval [RI] 175–600). Serum biochemical analysis revealed hypoglobulinemia (2.6 g/dl; RI 2.8–5.1). No other clinically significant abnormalities were noted. Total thyroxine was within the RI (1.7 µg/dl; RI 0.8–4.7). At the second visit, a recheck CBC showed progressive thrombocytopenia (136×10^3/µl) and a mild decrease in hematocrit (41.9%; RI 30–50) (Table 1). The hypoglobulinemia had resolved (3.8 g/dl) (Table 2). Outpatient care with subcutaneous (SC) fluids, an SC injection of maropitant (Cerenia; Zoetis) and transdermal mirtazapine (Mirataz; Dechra) was pursued without clinical improvement.

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Table 1 Select complete blood count data on initial presentation to the referring veterinary hospital (day 1) and on follow-up examination 2 days later (day 3)

	Day 1	Day 3	Reference interval
Hematocrit (%)	46.4*	41.9	30–45
Leukocytes (10³/µl)	6.44	6.02 K/µl	5.50–19.5
Neutrophils (10³/µl)	4.35	4.49 K/µl	2.50–12.5
Lymphocytes (10³/µl)	1.28	0.88	0.40–6.80
Monocytes (10³/µl)	0.48	0.38	0.15–1.70
Eosinophils (10³/µl)	0.32	0.25	0.10–0.79
Basophils (10³/µl)	0.01	0.02	0.00–0.10
Platelets (10³/µl)	169*	136 K/µl*	175–600

*Abnormal value

Table 2 Select serum biochemical values on initial presentation to the referring veterinary hospital (day 1) and on follow-up examination 2 days later (day 3)

|	Day 1	Day 3	Reference interval
Creatinine (mg/dl)	1.6	1.3	0.8–2.4
Blood urea nitrogen (mg/dl)	23	23	16–36
Albumin (g/dl)	3.3	2.9	2.2–4.0
Globulin (g/dl)	2.6*	3.8	2.8–5.1
Sodium (mmol/l)	154	153	150–165
Potassium (mmol/l)	4.2	3.7	3.5–5.8
Chloride (mmol/l)	115	112	112–129

*Abnormal value

On presentation, the patient was quiet, hypothermic (36.8°C; RI 38.3–39.2) and tachypneic with a respiratory rate of 40 breaths/min (RI 16–40). Muffled heart sounds were appreciated. The remainder of the physical examination was unremarkable. A venous blood gas analysis (Nova Biomedical) was performed and revealed normal acid–base status, mild hyponatremia (137.2 mmol/l; RI 149–160) and mildly elevated creatinine (1.4 mg/dl; RI: 0.3–1.3). Presenting packed cell volume (PCV) was within normal limits (40%; RI 28–50) and total solids (TS) were mildly decreased (5.6 g/dl; RI 6–8.6). A manual platelet estimate was 150–225 × 10³/µl, with multiple platelet clumps. Both thoracic-and abdominal-focused assessment with ultrasonography for trauma (TFAST and AFAST, respectively) were performed as described by Lisciandro.[1] Moderate pleural effusion was noted at all thoracic sites and pericardial effusion (PCE) was identified at the diaphragmaticohepatic view. There was no evidence of cardiac tamponade or peritoneal effusion. An electrocardiogram revealed normal sinus rhythm. Thoracic radiographs revealed a moderate volume of pleural effusion, PCE, cardiomegaly and mild hepatomegaly.

The patient received intravenous (IV) injections of furosemide (2 mg/kg) and maropitant (1 mg/kg). The patient was sedated with butorphanol (0.2 mg/kg) IV and alfaxalone (0.5 mg/kg) and a right-sided pericardiocentesis was performed to yield 90 ml grossly serosanguineous fluid. The PCV and TS of the pericardial fluid were 13% and 4.6 g/dl, respectively. An additional 145 ml serosanguineous fluid was removed via right-sided pleurocentesis, with a PCV and TS of 3% and 2.6 g/dl, respectively. Both effusions were cytologically evaluated by the attending clinician and described similarly despite the difference in PCV and TS. Both were composed primarily of neutrophils and macrophages. No microorganisms were noted. The patient was hospitalized for oxygen therapy (fraction of inspired oxygen [FiO$_2$] 40%). A recheck TFAST performed overnight revealed recurrence of PCE without cardiac tamponade, and a static, small volume of pleural effusion.

The following day a brief echocardiogram performed by a board-certified internal medicine specialist confirmed the presence of mild-to-moderate PCE in the absence of left atrial enlargement (left atrial diameter 1.47 cm; RI 1.03–1.71)[2] or systolic dysfunction, as indicated by normal fractional shortening (68%; RI: 40–66.7) (Figure 1).[2] A 4 cm mass lesion was noted in the left pericardial space, with differentials including hematoma following pericardiocentesis, infiltrative pericardial disease, granulomatous disease, neoplasia or infectious/inflammatory pericarditis (Figure 2). Both SNAP 4Dx Plus and SNAP FIV/FeLV Combo tests (IDEXX) were negative. A vector-borne panel was submitted to the North Carolina
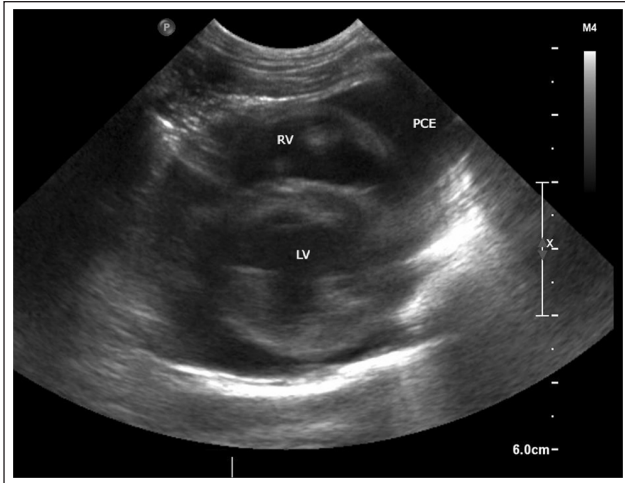
Figure 1 Right parasternal short-axis echocardiographic image revealing mild-to-moderate pericardial effusion. RV = right ventricle; LV = left ventricle; PCE = pericardial effusion
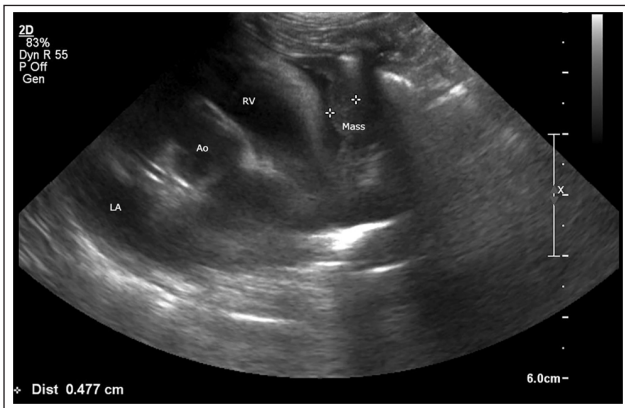
Figure 2 Right parasternal short-axis echocardiographic image revealing a mass in the pericardial space; markers indicate a measurement of 0.477 cm in this plane. LA = left atrium; Ao = aorta; RV = right ventricle

Table 3 Two-dimensional echocardiographic parameters obtained by a board-certified cardiologist after the cat in this report had been hospitalized for 48 h

	Measurement	Reference interval[2]
Ao diameter (cm)	1.3	0.81–1.39
LA diameter (cm)	1.4	1.03–1.71
LA: Ao	1.10	0.86–1.84

LA = left atrium; Ao = aortic root; LA: Ao = left atrial-to-aortic root ratio

Table 4 M-mode echocardiographic parameters obtained by a board-certified cardiologist after the cat in this report had been hospitalized for 48 h

	Measurement	Reference interval[2]
IVSd (cm)	0.60	0.30–0.60
LVIDd (cm)	1.30	1.08–2.14
LVPWd (cm)	0.60	0.25–0.60
IVSs (cm)	1.0	0.40–0.90
LVIDs (cm)	0.40	0.40–1.12
LVPWs (cm)	1.0	0.43–0.98
%FS	72	40–66.7

IVSd = interventricular septal diameter in diastole; LVIDd = left ventricular internal diameter in diastole; LVPWd = left ventricular posterior wall thickness in diastole; IVSs = interventricular septal diameter in systole; LVIDs = left ventricular internal diameter in systole; LVPWs = left ventricular posterior wall thickness in systole; %FS = percentage fractional shortening, determined using the equation $100 \times (LVIDd - LVIDs)/LVIDd$

State University Vector Borne Disease Lab, including PCR assays for *Anaplasma* species, *Babesia* species, *Bartonella* species, *Cytauxzoon* species, *Ehrlichia* species, hemotropic *Mycoplasma* species, *Rickettsia* species and immunofluorescence assays for *Bartonella* species. Doxycycline (6 mg/kg PO q12h) and marbofloxacin (25 mg PO q24h) were started empirically. The patient was eupneic and normothermic at an FiO_2 of 40% but remained hyporexic.

Forty-eight hours after initial presentation, a complete echocardiogram was performed by a board-certified cardiologist, confirming normal left atrial size (Table 3), systolic function (Table 4) and the presence of PCE. Structural cardiac changes included mild left ventricular hypertrophy, mild thickening of the aortic valve with a nodular intravalvular lesion and an intrapericardial mass-like lesion.

Compared with images from the abbreviated echocardiogram performed the previous day, the pericardial mass was described as progressive and more extensive (measurement not provided). The presence of a thickened aortic valve with a nodular appearance raised further concern for an infectious or inflammatory process. Cefovecin (8 mg/kg SC [Convenia; Zoetis]) was administered to broaden the spectrum of antibiotic coverage while appetite was poor. Ondansetron (0.2 mg/kg IV q12h), maropitant (1 mg/kg IV q24h) and mirtazapine (3.75 mg PO every other day) were continued due to persistent hyporexia. Given normal systolic function and persistent inappetence, IV fluid therapy was initiated at 60 ml/kg daily.

The following day, a recheck echocardiogram was performed by the same cardiologist. The previously described intrapericardial mass lesion had nearly doubled in size and was newly adhered to both the epicardium and pericardium. In some images, the lesion had a striated appearance and granulomatous etiology was further considered. Large-volume PCE with new cardiac tamponade was present. Given clinical decline and recurrence of effusion, thoracic CT for surgical planning and metastases screening, followed by pericardiectomy and epicardial mass resection, was offered. Owing
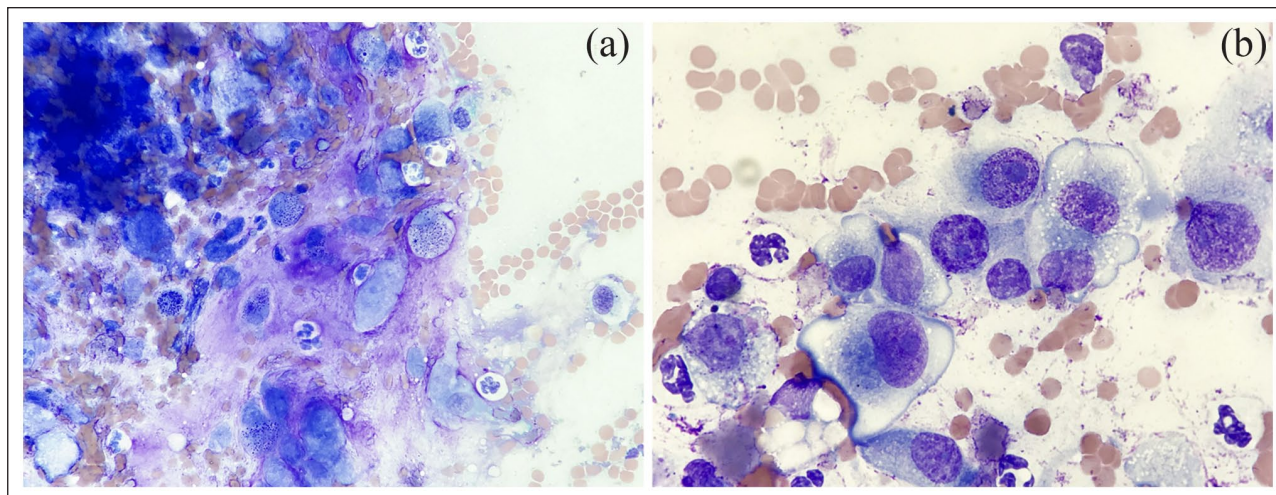
Figure 3 (a) Photomicrograph of an impression smear from the nodular epicardial lesion illustrates a population of atypical, round to spindloid mesenchymal cells admixed with brightly eosinophilic matrix. These cells occasionally contain dark-pink cytoplasmic granules. Mild neutrophilic inflammation is present. (b) Photomicrograph of the same preparation illustrates the cytologic detail of the neoplastic population, including anisocytosis, anisokaryosis, binucleation and large, distinct nucleoli. Erythrophagia is present (lower left corner). Wright-Giemsa stain

to owner concerns regarding treatment and prognosis, the cat was euthanized.

Post-mortem samples of the aortic valve, myocardium, pericardium and a sample of PCE were submitted for diagnostic evaluation. Gross evaluation of the tissues revealed a firm, pale, nodular and coalescing mass structure with opaque and dark-purple discolorations extending circumferentially around the heart base and intrapericardial space. The aortic valve appeared grossly normal. An impression smear of the nodular epicardial lesion was submitted for cytologic evaluation while histopathologic evaluation was pending (Figure 3). The sample was composed of markedly atypical mesenchymal cells admixed with eosinophilic matrix, an increased number of neutrophils and erythrophagocytic and hemosiderin laden macrophages. The cytologic diagnosis was sarcoma with evidence of chronic, active hemorrhage and mild neutrophilic inflammation. The PCE sample was hemorrhagic with a few clusters of the neoplastic cells admixed with eosinophilic matrix.

Histopathologic evaluation of the myocardial and pericardial tissues revealed pleomorphic neoplasia with mild myocardial invasion, with differentials including histiocytic sarcoma, pleomorphic mesothelioma and pleomorphic sarcoma (Figure 4). The echocardiographic lesion described on the aortic valve was not identified, although adherent fibrin was noted. Blood and tissue cultures were not performed.

For further characterization of the neoplasm, IHC was pursued. IHC staining for cytokeratin and ionized calcium-binding adapter molecule-1 did not stain the neoplastic population, thus excluding mesothelioma
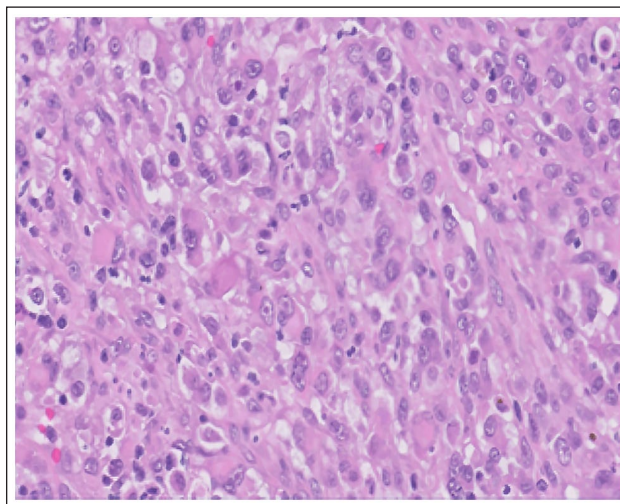
Figure 4 Photomicrograph of histopathologic findings from sections of grossly identified pericardial nodules, illustrating highly atypical malignant spindle-to-round cells which, in some areas, become very pleomorphic, demonstrating severe anisocytosis, anisokaryosis and multinucleation

and histiocytic neoplasia.[3,4] Given these exclusions, the sarcoma was described as a pleomorphic sarcoma of unspecified origin.

The vector-borne infectious disease panel returned post mortem and showed positive *Bartonella henselae* PCR and elevated bartonellosis titers. *Bartonella* species immunofluorescence assay titers were elevated for three species, including 1:128 for *Bartonella vinsonii*, 1:512 for *B a henselae* and 1:1024 for *Bartonella koehlerae*. The contribution of bartonellosis in this patient's clinical

course is unknown but is presumed unrelated to the diagnosis of sarcoma.

Discussion

Pericardial disease in cats is rare, as is the development of PCE and cardiac tamponade.[5,6] The reported causes of pericardial disease and PCE in cats include congestive heart failure (CHF), neoplasia, feline infectious peritonitis, peritoneopericardial diaphragmatic hernia, systemic infections, disseminated intravascular coagulation, uremia, bacterial pericarditis and idiopathic.[5–7] A study by Davidson et al[5] investigated the cause of PCE in 83 cats and determined that the most common cause was CHF (n = 37/83; 45%), followed by neoplasia (n = 16/83; 19%). Similarly, Hall et al[6] evaluated the etiology of PCE in 164 cats and confirmed the two most common causes as CHF (75%) and neoplasia (5.4%). The most common neoplasm identified in that study was lymphosarcoma. Multiple other sources confirm the most common cardiac neoplasm to be lymphosarcoma.[8–10] Reports of non-lymphomatous pericardial neoplasms include intrapericardial ectopic thyroid carcinoma, primary cardiac rhabdomyosarcoma, chemodectoma, mesothelioma, primary and metastatic hemangiosarcoma, fibrosarcoma, multiple myeloma, carcinoid carcinomatosis, aortic body carcinoma, multiple metastatic carcinoma and primary myocardial sarcoma.[5,6,8,11–13]

Undifferentiated pleomorphic sarcoma (UPS), previously referred to as malignant fibrous histiocytoma, is a mesenchymal neoplasm that has been well documented in human medicine. Tumors classified as UPS have a pleomorphic spindle cell population and are characterized by the absence of an identifiable line of differentiation either morphologically or immunohistochemically.[14] They are often associated with regional hemorrhage and necrosis, and occasionally have an associated lymphohistiocytic infiltrate.[15] UPS is the third most common soft tissue sarcoma in adult humans, and is typically found on the head, neck, trunk, extremities and retroperitoneum.[15] Similarly, a recent retrospective study by de Cecco et al[16] evaluating the pathologic and immunohistochemical characteristics of pleomorphic sarcoma in 13 adult feline patients identified this neoplasm in the flank, lateral thorax, limbs and interscapular region. The presence of this neoplasm in a visceral organ was not reported.

In human medicine, cardiac UPS is an incredibly rare entity. The overall incidence of primary cardiac tumors in humans is 0.002–0.3%.[17] Approximately 25% of these tumors are malignant, of which approximately 95% are sarcomas.[15,17] Twelve percent of all cardiac sarcomas are UPS. In pediatric patients, the most common primary cardiac malignancy is also sarcoma, with only rare case reports of UPS.[18] Cardiac UPS is aggressive and locally invasive, making complete surgical excision difficult.[18,19]

Even with complete surgical resection, this malignancy carries a median survival time of 6–12 months, as recurrent disease develops rapidly.[19] As the owners of this patient elected not to pursue thoracotomy and instead chose humane euthanasia, we are unable to comment on treatment responsiveness or outcome.

Infectious disease testing was performed due to concerns for infectious endocarditis and/or myocarditis. Given the ultimate diagnosis of epicardial neoplasia, the post-mortem evidence of an active *Bartonella* species infection was unexpected. A recent study demonstrated an association between *Bartonella* species infection and the development of neoplastic and non-neoplastic vasoproliferative lesions in both animals and humans.[20] In that study, the molecular prevalence of *Bartonella* species, *Babesia* species and hemotropic *Mycoplasma* species in dogs with hemangiosarcoma was investigated. *Bartonella* species DNA was amplified from 73% (n = 80/110) of dogs with hemangiosarcoma. An in vitro study wherein macrophages were infected with *B henselae* demonstrated that the organism triggers production of vascular endothelial growth factor and can therefore contribute to proliferation of endothelial cells.[21] At present, however, there are no reports in the human or veterinary literature supporting a connection between infection with *Bartonella* species and the development of other, non-vasoproliferative forms of neoplasia.

Conclusions

Although an uncommon etiology, this case provides a new differential for PCE in cats, particularly in the presence of a mass lesion. The diagnosis of this neoplasm in the epicardium is a novel manifestation of this disease in the feline patient. Given the recent retrospective study supporting similar findings between this type of neoplasia in feline and human patients, further information about UPS may support extrapolation from human literature regarding treatment, prognosis and application to the feline patient.

('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

References

1   Lisciandro G. **Abdominal and thoracic focused assessment with sonography for trauma, triage, and monitoring in small animals.** *J Vet Emerg Crit Care* 2001; 21: 104–122.
2   Drourr L, Lefbom BK, Rosenthal SL, et al. **Measurements of M-mode echocardiographic parameters in healthy adult Maine Coon cats.** *J Am Vet Med Assoc* 2005; 226: 734–737.
3   Painter JT, Clayton NP and Herbert RA. **Useful immunohistochemical markers of tumor differentiation.** *Toxicol Pathol* 2010; 38: 131–141.
4   Pierezan F, Mansell J, Ambrus A, et al. **Immunohistochemical expression of ionized calcium binding adapter molecule 1 in cutaneous histiocytic proliferative, neoplastic and inflammatory disorders of dogs and cats.** *J Comp Pathol* 2014; 151: 347–351.
5   Davidson BJ, Paling AC, Lahmers SL, et al. **Disease association and clinical assessment of feline pericardial effusion.** *J Am Anim Hosp Assoc* 2008; 44: 5–9.
6   Hall DJ, Shofer F, Meier CK, et al. **Pericardial effusion in cats: a retrospective study of clinical findings and outcome in 146 cats.** *J Vet Intern Med* 2007; 21: 1002–1007.
7   LeBlanc N and Scollan KF. **Bacterial pericarditis in a cat.** *JFMS Open Rep* 2015; 1. DOI: 10.1177/2055116915603077.
8   Ware WA. **Cardiac neoplasia.** In: Bonagura JD (ed). Kirk's current veterinary therapy. Vol. XII. Philadelphia, PA: WB Saunders, 1995, pp 873–876.
9   Treggiari E, Pedro B, Dukes-McEwan J, et al. **A descriptive review of cardiac tumours in dogs and cats.** *Vet Comp Oncol* 2015; 15: 273–288.
10 Aupperle H, Marz I, Ellenberger C, et al. **Primary and secondary heart tumours in dogs and cats.** *J Comp Pathol* 2007; 136: 18–26.
11 Knowles S, Uhl EW, Blas-Machado U, et al. **Intrapericardial ectopic thyroid carcinoma in a cat.** *J Vet Diag Invest* 2010; 22: 1010–1013.
12 Venco L, Kramer L, Sola LB, et al. **Primary cardiac rhabdomyosarcoma in a cat.** *J Am Anim Hosp Assoc* 2001; 37: 159–163.
13 Shinohara N, Macgregor JM, Calo A, et al. **Presumptive primary cardiac lymphoma in a cat causing pericardial effusion.** *J Vet Cardiol* 2005; 7: 65–69.
14 DeFilippis EM, Nohria A, Burstein HJ, et al. **A breathtaking diagnosis.** *N Engl J Med* 2019; 380: 81–87.
15 Henderson MT and Hollmig ST. **Malignant fibrous histiocytoma: changing perceptions and management challenges.** *J Am Acad Derm* 2012; 67: 1335–1341.
16 de Cecco BS, Argenta FF, Bianchi RM, et al. **Feline giant-cell pleomorphic sarcoma: cytologic, histologic and immunohistochemical characterization.** *J Feline Med Surg* 2020; 23: 738–744.
17 Randhawa JS, Budd GT, Randhawa M, et al. **Primary cardiac sarcoma.** *Am J Clin Oncol* 2016; 39: 593–599.
18 Tzani A, Doulamis IP, Mylonas KS, et al. **Cardiac tumors in pediatric patients: a systematic review.** *World J Pediatr Congenit Heart Surg* 2017; 8: 624–632.
19 Vaitiekiene A, Vaitiekus D, Urbonaite L, et al. **Multidisciplinary approach to rare primary cardiac sarcoma: a case report and review.** *BMC Cancer* 2019; 19: 529.
20 Lashnits E, Neupane P, Bradley JM, et al. (2020) **Molecular prevalence of *Bartonella*, *Babesia*, and hemotropic *Mycoplasma* species in dogs with hemangiosarcoma from across the United States.** *PLoS One* 2020; 15. DOI: 10.1371/journal.pone.0227234.
21 Beerlage C, Varanat M, Linder K, et al. *Bartonella vinsonii* **subsp. berkhoffii and *Bartonella henselae* as potential causes of proliferative vascular diseases in animals.** *Med Microbiol Immunol* 2012; 201: 319–326.